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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,197	01/10/2002	Mario Stevenson	07917-089002	3670

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	4

DATE MAILED: 09/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,197	STEVENSON, MARIO	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 1, is attached to the instant Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 11, 12 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what is meant "wherein RNA can not be detected", this term ambiguous in that determining the presence of viral RNA depends on the detection method used and the sample applied.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zazzi et al. (Journal of Medical Virology, 1997) and Bissete et al. (Journal of Medical Virology 1997) in view of Bukrinsky et al. (PNAS, 1992).

The present invention is directed at detecting HIV infection in a mammal by detecting the presence of 2-LTR circle DNA in a population of cells. The mammal is undergoing combination anti-HIV drug therapy, which by definition (see specification page 3, line 18-24) is defined as the administration of two or more antiretroviral compounds. The detection is accomplished using PCR amplification and hybridization. The invention also discloses specific primers spanning 9591-9610 and 9650-9669 of the HXB2 strain of HIV-1.

Zazzie et al. teach a method of detecting 2-LTR circle DNA from the PBMC isolated DNA of HIV seropositive individuals (see materials and methods). PBMC were lysed using SDS and proteinase K followed by phenol chloroform extraction and ethanol precipitation. Purified DNA was subjected to PCR amplification using LTR-LTR junction specific primers. The reference teaches using this detection method on subjects that have been treated with a single antiretroviral compound (see table 2). The reference teaches that not all seropositive individuals will also be positive for 2-LTR. The primary teaching from Zazzie et al. is that 2-LTR can be detected from PBMC of HIV seropositive individuals, including individuals

subjected to monotherapy with an anti-retroviral compound (AZT a reverse transcriptase inhibitor).

Bisset et al. teach the use of highly active antiretroviral therapy (HAART) for treatment early during the HIV infection. HAART therapy during the asymptomatic HIV infection phase is observed with decreased plasma RNA levels while increasing the CD4:CD8 ratios. The drug combination includes reverse transcriptase inhibitors and protease inhibitors. The lesson from Bisset et al. is that HAART therapy is very effective at reducing viral RNA load in the serum. The reference does not teach using 2-LTR circular DNA as a marker for viral infection.

Bukrinskey et al. teach a method of detecting 2-LTR circular DNA in *in vitro* HIV infected cells. The method sets forth the specific primers claimed in claim 21. The reference does not teach the use of 2-LTR circular DNA as a method of identifying HIV infected cells from a patient sample.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize combination drug therapy in the treatment of HIV disease as taught by Bisset et al., and apply the new detection method as taught by Zazzie et al. One having ordinary skill in the art would have been motivated to monitor antiretroviral therapies at the molecular level, rather than the CD4 cell count, in order to make changes in the drug combination treatment as new resistant viral variants emerge. This information is clinically valuable by providing reliable assessment of the viral burden and is useful in monitoring the clinical efficacy of the treatment. Bukrinskey et al. teach specific PCR primers for the detection of the 2-LTR circular DNA. Zazzie et al. also use PCR detection for the isolation of the 2-LTR, although the particular primers are located in the same general area there can be great variability in primers which still

are able to detect the 2-LTR circular DNA. Therefore, the selection of a specific primer set would fall under optimizing experimental conditions by the ordinary artisan. If a specific primer should produce an unexpected result, such as improved detection of the 2-LTR circular DNA as compared to the prior art, applicant needs to point out what these unexpected results are.

Therefore, the instant invention is obvious in view of Zazzi et al., Bissete et al. and Bukrinsky et al.

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zazzi et al. (Journal of Medical Virology, 1997) and Chun et al. (PNAS 1997) in view of Bukrinsky et al. (PNAS, 1992).

The present invention is directed at detecting HIV infection in a mammal by detecting the presence of 2-LTR circle DNA. The mammal is undergoing combination anti-HIV drug therapy, which by definition (see specification page 3, line 18-24) is defined as the administration of two or more antiretroviral compounds. The detection is accomplished using PCR amplification. The invention also discloses specific primers spanning 9591-9610 and 9650-9669 of the HXB2 strain of HIV-1.

Zazzie et al. teach a method of detecting 2-LTR circle DNA from the PBMC isolated DNA of HIV seropositive individuals (see materials and methods). PBMC were lysed using SDS and proteinase K followed by phenol chloroform extraction and ethanol precipitation. Purified DNA was subjected to PCR amplification using LTR-LTR junction specific primers. The reference teaches using this detection method on subjects that have been treated with a single antiretroviral compound (see table 2). The reference teaches that not all seropositive

individuals will also be positive for 2-LTR. The main teaching from Zazzie et al. is that 2-LTR can be detected from PBMC of HIV seropositive individuals, including individuals subjected to monotherapy with an anti-retroviral compound (AZT a reverse transcriptase inhibitor).

Chun et al. teach patients on HAART therapy with undetectable levels of plasma HIV RNA harbor resting cells that contain integrated HIV-1 DNA (see page 13195, column 1, first paragraph). The integrated HIV DNA was assayed using PCR (see figurer 1). Replication-competent virus was induced from resting CD4+ T cells in whom plasma viremia was undetectable by plasma RNA levels. The data suggest that unintegrated HIV-1 DNA contributed to the inducible virus (see page 13197, column 1, lines 5-28). The reference does not teach detecting 2-LTR circular DNA in samples from patients that have no detectable cell-free HIV RNA.

Bukrinskey et al. teach a method of detecting 2-LTR circular DNA in *in vitro* HIV infected cells. The method sets forth the specific primers disclosed in the specification. The reference does not teach the use of 2-LTR circular DNA as a method of identifying HIV infected cells from a patient.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize combination drug therapy in the treatment of HIV disease as taught by Chun et al., and apply the new detection method as taught by Zazzie et al. One having ordinary skill in the art would have been motivated to monitor antiretroviral therapies at the molecular level, rather than the CD4 cell count, in order to make changes in the drug combination treatment as new resistant viral variants emerge. This information is clinically valuable by providing reliable assessment of the viral burden and is useful in monitoring the clinical efficacy of the treatment.

Bukrinskey et al. teach specific PCR primers for the detection of the 2-LTR circular DNA. Zazzie et al. also use PCR detection for the isolation of the 2-LTR, although the particular primers are located in the same general area there can be great variability in primers which still are able to detect the 2-LTR circular DNA. Therefore, the selection of a specific primer set would fall under optimizing experimental conditions by the ordinary artisan. If a specific primer should produce an unexpected result, such as improved detection of the 2-LTR circular DNA as compared to the prior art, applicant needs to point out what these unexpected results are.

Therefore, the instant invention is obvious in view of Zazzi et al., Chun et al. and Bukrinsky et al.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 or for informal communications use 703-746-3162.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER

9/5/03